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Thromboembolic events and Covid-19

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ABSTRACT

The novel Corona virus infection (Covid-19) first identified in China in December 2019 has rapidly progressed in pandemic leading to significant mortality and unprecedented challenge for healthcare systems. Although the clinical spectrum of Covid-19 is variable, acute respiratory failure and systemic coagulopathy are common in severe Covid-19 patients. Lung is an important target of the SARS-CoV-2 virus causing eventually acute respiratory distress syndrome associated to a thromboinflammatory state. The cytokinic storm, thromboinflammation and pulmonary tropism are the bedrock of tissue lesions responsible for acute respiratory failure and for prolonged infection that may lead to multiple organ failure and death. The thrombogenicity of this infectious disease is illustrated by the high frequency of thromboembolic events observed even in Covid-19 patients treated with anticoagulation. Increased D-Dimers, a biomarker reflecting activation of hemostasis and fibrinolysis, and low platelet count (thrombocytopenia) are associated with higher mortality in Covid-19 patients. In this review, we will summarize our current knowledge on the thromboembolic manifestations, the disturbed hemostatic parameters, and the thromboinflammatory conditions associated to Covid-19 and we will discuss the modalities of anticoagulant treatment or other potential antithrombotic options.

1. Introduction

Compared with severe acute respiratory syndrome coronavirus (SARS-CoV-1) and Middle East respiratory syndrome (MERS-CoV), the novel corona virus infection (Covid-19), which first case was described in China in December 2019, has spread more rapidly and the epidemic has unevenly affected nearly all continents. This new disease has made more than 370000 confirmed victims worldwide at the end of May 2020, probably underestimated due to weaknesses in the census or the lack of publications. Around 5–10% of Covid-19 patients are severely affected and admitted to intensive care unit (ICU) for mechanical ventilation because of pneumonia. The pathophysiology of SARS-CoV-2 infection goes far beyond the only pulmonary attack and is still under characterization. This review will focus on the thromboembolic events frequently observed in severe Covid-19 patients. It is mainly based on publications of isolated clinical cases or short series, with a retrospective collection of data, still rare histopathological data, and as far as our subject is concerned, results of fairly standard routine tests, and antithrombotic treatment practices by analogies with other pathologies,

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which have been adapted over the course of experience.

2. Clinical manifestation of thromboembolic complications in Covid-19

From the first cases of the disease, symptoms of severe acute respiratory infection accompanied by acute respiratory distress syndrome (ARDS) revealed the lung tropism of this new virus. Autopsy studies of Covid-19 patients (Fox et al., 2020; Wichmann et al., 2020) confirm that lung is a major target organ for SARS-CoV-2, although other organ failure (heart, kidney) and neurological disorders may be observed (Guan et al., 2020; Huang et al., 2020). The SARS-CoV-2 virus uses ACE2 (angiotensin-converting enzyme 2) receptor expressed by pneumocytes in the epithelial alveolar lining to infect the host's lung. Around 5–10% of Covid-19 patients need hospitalization in ICU and require mechanical ventilation. Associated with the severe lung disease, cases of Covid-specific coagulopathy were first reported in China and then all over the world (Wang et al., 2020a; Tang et al., 2020a; Connors and Levy, 2020). The patients presenting with more severe disease symptoms had more pronounced coagulopathy associated with a pejorative prognosis. Severe Covid-19 patients are prone to develop thrombotic events including pulmonary embolism (PE), deep vein thrombosis (DVT), arterial thrombosis and intracatheter thrombosis (Klok et al., 2020a; Helms et al., 2020; Lodigiani et al., 2020; Bikdeli et al., 2020; Joly et al., 2020; Ranucci et al., 2020). Cases of disseminated intravascular coagulopathy (DIC) are also described. This increased Covid-19 patient's predisposition to thrombotic diseases has been highlighted in recent reviews (Connors and Levy, 2020; Bikdeli et al., 2020). Of note, the thrombotic risk is influenced by race and ethnicity and is significantly lower in Chinese compare to Caucasian individuals (Fogarty et al., 2020).

Patients with infection by pathogens admitted to ICU for sepsis are known to frequently develop thromboembolic events that contribute to multi-organ failure. The International Society on Thrombosis and Haemostasis (ISTH) has individualized this medical entity under the acronym sepsis-induced coagulopathy (SIC) and developed a SIC score along with a DIC score. This ISTH definition has been used in reports concerning the Covid-19 patients presenting coagulopathy. Some specificities of SARS-CoV-2 infection induced coagulopathy have however stimulated the emergence of other acronyms like pulmonary intravascular coagulopathy (PIC) (Fogarty et al., 2020) which, given the tropism and viral involvement, would be appropriate, or Covid-19 associated coagulopathy (CAC) which is now frequently used.

The first experiences in the Wuhan province in China, and then in other parts of the world, reported in the form of retrospective and then prospective studies, allowed to propose an incidence of thromboembolic complications ranging from around 15% to 85%, depending on the diagnostic mode (systematic screening or clinical manifestation) and on the severity of the patient population studied (ICU or traditional hospitalization). In these first studies, the size of the patient cohorts for which the incidence of thrombotic events has been quantified was rather small with a probable overestimation of the actual rates of thrombosis all causes included. The nature of thromboembolic episodes was not always precisely specified, and the terms “any cause” or “cumulative incidence” have been used in several reports (Middeldorp et al., 2020). Nevertheless, the multiplicity of these studies, combined with post-mortem analyses have led to a better understanding of the pathogenesis and strongly supports the association between Covid-19 and

Table 1

Incidence of venous thromboembolic events among the different studies.

References	Patient number and setting	Thromboembolic events	Study relevance
Cui et al. (2020)	81, ICU	Incidence of VTE is 25%	Retrospective and single-center study
Demelo-Rodriguez et al. (2020)	156, non ICU	Incidence of asymptomatic DVT is 15%	Prospective and single-center study
Helms et al. (2020)	150, ICU	43% of VTE of which 17% is PE	Prospective and multicentric study
Klok et al. (2020a)	184	Cumulative incidence of VTE of 31% (CTPA confirmed in 27%) of which 81% is PE	Prospective and multicentric study
Llitjos et al. (2020)	26, ICU	Cumulative incidence of peripheral VTE of 69% of which 23% is PE	Retrospective and single-center study
Lodigiani et al. (2020)	388	Cumulative rate of VTE is 21% (28% in ICU and 7% in the general ward)	Retrospective and single-center study
Marone and Rinaldi (2020)	30, non ICU	53% with positive signs or symptoms suggestive of DVT	Retrospective and single-center study
Middeldorp et al. (2020)	198	Cumulative incidence of VTE is 26% at D7, 47% at D14, 59% at D21 in ICU	Retrospective and single-center study
Poissy et al. (2020)	107, ICU	Cumulative incidence of PE is 21%	Retrospective and single-center study
Ren et al. (2020)	48, ICU	86% of lower extremity DVT of which 75% are distal and 10% proximal	Retrospective and multicentric study
Spiezia et al. (2020)	22, ICU	23% of DVT	Retrospective and single-center study
Zhang L et al. (2020a)	143	47% developed lower extremity DVT (35% proximal and 65% distal)	Retrospective and single-center study

ICU, intensive care unit; VTE, venous thromboembolism; DVT, deep vein thrombosis; CTPA, computed tomography pulmonary angiogram; PE, pulmonary embolism; D, day.

coagulopathy (Table 1).

Klok et al. reported a high percentage of PE (Klok et al., 2020b) but other studies report that PE does not seem to be a primary mechanism in contrast to DVT (Helms et al., 2020; Lodigiani et al., 2020).

DIC may complicate SARS-CoV-2 infection (Lillicrap, 2020). Tang and colleagues (Tang et al., 2020a) revealed that 71.4% of the non-survivors from Covid-19 matched the grade of overt-DIC in comparison with survivors (0.6%) according to ISTH criteria (Levi et al., 2009). It has been suggested that DIC might not be only a concomitant finding of Covid-19, but is part of the process leading to organ failure with microthrombi and tissue damage (Seitz and Schramm, 2020). It is still unclear whether DIC results from the progression of the early coagulation changes in Covid-19. Recently, it was proposed that thrombosis occurs within the pulmonary circulation, in the absence of apparent embolism, due to *in situ* macro and microthrombi formation (Deshpande, 2020). Whether the presence of these thrombi correlates with the presence of DIC during SARS-CoV-2 infection is unknown.

Autopsy reports provided important information and demonstrated thrombotic microangiopathy (Wichmann et al., 2020; Konopka et al., 2020; Menter et al., 2020). A German prospective series including 12 Covid-19 patients found a high incidence of DVT (58%) and PE in 4 patients as a direct cause of death (Wichmann et al., 2020). Histopathological study of the lungs revealed diffuse alveolar damage, as classically described in ARDS (Thompson et al., 2017), associated with the presence of microthrombi in small caliber pulmonary vessels. A Swiss autopsy report of 21 patients also revealed diffuse alveolar damage, significant pulmonary capillary congestion, the presence of fibrin deposits and microthrombi despite well-conducted anticoagulation in these patients (Menter et al., 2020). A French series based on 5 autopsies discusses the histological pattern of acute fibrinous and organizing pneumonia in Covid-19 patients with accumulation of intra-alveolar fibrin deposits (Copin et al., 2020). Overall, it appears that DVT and thrombotic microangiopathy of the pulmonary capillaries are more frequently observed in severe SARS-CoV-2 infection than PE. As discussed below, different mechanisms may occur according to vascular territories, the caliber of the vessels and their sensitivity to the highly inflammatory environment.

Arterial territories of all calibers seem less prone to embolic episodes since infarction, lower limb ischemia, mesenteric ischemia and stroke are under-represented (Helms et al., 2020; Lodigiani et al., 2020; Kashi et al., 2020).

Of note, “chilblains like” skin lesions have also been reported whose physiopathology is still debated (De Masson et al., 2020) but the hypothesis of an acro-ischemic lesion has been suggested following observation of microthrombi in rare skin biopsies (Piccolo and Bassi, 2020; Fernandez-Nieto et al., 2020), again pointing to the potential tropism of the virus for small vessels.

3. Disturbed hemostasis parameters in Covid-19

Covid-19 patients with coagulopathy being at increased risk of mortality (Tang et al., 2020a; Zhou et al., 2020), it is important to monitor biological and hemostatic changes during the course of the disease. The most frequently reported changes are an increase in D-dimer levels (a degradation products of fibrin acting as a biomarker reflecting fibrin formation and fibrinolysis), a moderate thrombocytopenia, and a slight prolonged prothrombin time. Early in the epidemic, Huang et al. described that Covid-19 patients hospitalized in the ICU have significantly higher levels of D-dimer compared to Covid-19 patients not admitted in ICU (Huang et al., 2020). Moreover, in a cohort of 191 patients, it was shown that D-dimer levels > 1 mg/L were significantly associated with an increase in hospital mortality (Zhou et al., 2020). In a chinese cohort of 1099 patients, 46.4% of the patients had D-dimer levels > 0.5 mg/L (Guan et al., 2020).

Prothrombin time was significantly longer in IUC compared to non-IUC Covid-19 patients, but the absolute difference was small (Huang et al., 2020). Accordingly, prothrombin time was significantly longer in non-survivors compared to survivors (Tay et al., 2020).

Unlike patients conventionally admitted to ICU for septic shock, where thrombocytopenia is often deep, long-lasting and correlates with morbidity and mortality (Akca et al., 2002), it appears to be moderate in SARS-CoV-2 infection. Indeed, Huang et al. report 5% of patients with a platelet count < 100 G/L and 8% in patients admitted to ICU (Huang et al., 2020). The reasons for this relative preservation of platelet counts are unknown. Very low platelet counts (< 20 G/L) or sudden fall in platelet count suggest additional causes of thrombocytopenia (immune or drug-induced). Guan et al. found a 36.2% incidence of thrombocytopenia < 150 G/L, rising 57.7% in patients admitted to ICU (Guan et al., 2020). A meta-analysis of 9 studies with 1779 Covid-19 patients indicates that the most severe patients had lower platelet counts (Lippi et al., 2020). In a subgroup analysis of 4 studies, thrombocytopenia was associated with a 5-fold increased risk of developing severe Covid-19 (Guan et al., 2020; Huang et al., 2020; Zhou et al., 2020; Liu et al., 2020). Several mechanisms of thrombocytopenia in Covid-19 have been proposed (Xu et al., 2020a). Briefly, SARS-CoV-2 may reduce platelet production by infection of bone marrow cells, hemophagocytosis, or alteration of the pool of megakaryocytes present in the lungs. Other coronaviruses have been shown to infect the bone marrow resulting in hematopoiesis impairment (Yang et al., 2005a). SARS-CoV-2 virus may thus reduce platelet production by affecting megakaryopoiesis. Destruction of haematopoietic cells by activated macrophages may also occur leading to cytopenias including thrombocytopenia. The “cytokine storm” which has been widely discussed in the context of the Covid-19 epidemic appears to be associated in some patients with hemophagocytosis that may contribute to thrombocytopenia (Mehta et al., 2020). The SARS-CoV-2 virus may also increase platelet destruction with specific auto-destruction through autoantibodies and immune complexes similarly to other infections (Zulfiqar et al., 2020). Finally, the virus may increase platelet consumption via the formation of thrombi in the microcirculation as strongly suggested by autopsy reports showing the presence of platelet microthrombi in small caliber pulmonary vessels (Menter et al., 2020; Fox et al., 2020).

Fibrinogen levels during the course of Covid-19 are elevated (Tay et al., 2020; Panigada et al., 2020; Maier et al., 2020; Spiezia et al., 2020), particularly in ARDS (Ranucci et al., 2020), as expected in any strong inflammatory syndrome, but in contrast to

fibrinogen degradation products (D-Dimers), it is not a marker of poor prognosis (Tang et al., 2020a). Elevated fibrinogen may contribute to the plasma hyper-viscosity observed in Covid-19 patients (Maier et al., 2020), a factor known to increase endothelium damage and the risk of thrombosis.

In a series of 216 patients positive for SARS-CoV-2, 35 patients had prolonged activated partial thromboplastin time (APTT), uncorrected by mixture with normal plasma, and a lupus anticoagulant (LA) was found using clotting tests (dilute Russel Viper Venom Time and/or LA-sensitive APTT) (Bowles et al., 2020). Unfortunately, immunological testing (anticardiolipin, anti- β 2 glycoprotein-1) was not performed and LA could not be confirmed in the follow-up. The significance of this disorder is therefore difficult to assess, but these cases indicate that a prolonged APTT warrants complete exploration and is not *per se* an obstacle to anticoagulant treatment. Of note in a small series of 3 patients, ischemic stroke was associated to the presence of anticardiolipin and anti- β 2 glycoprotein-1 (Zhang et al., 2020b).

A moderated decrease in factor XII, a contact phase protein, was observed in 91% of patients who had a prolongation of the APTT. Contact pathway activation supports inflammation and thrombin generation and could play a role in immunothrombosis (Bowles et al., 2020), thus representing a potential therapeutic target in Covid-19 patients (Shatzel et al., 2020).

Severe Covid-19 patients have an endothelialopathy (endotheliitis) characterized by the accumulation of inflammatory cells and viral inclusions in endothelial cells (Becker, 2020). Laboratory parameters associated with endothelium activation, cell recruitment and activation may be lymphopenia, thrombocytopenia and elevated levels of Von Willebrand Factor (VWF) and factor VIII (FVIII). In a small series of severe Covid-19 patients, a massive elevation of VWF and FVIII levels was observed while ADAMTS13 activity (a disintegrin and metalloprotease known to regulate the size of VWF) was normal (Escher et al., 2020). It is interesting to note that a high VWF/ADAMTS13 ratio has already been associated with poor clinical outcome in acute ischemic brain injury (Taylor et al., 2020).

Another approach to demonstrate a hypercoagulability state of SARS-CoV-2 infection consists in the use of thromboelastography (TEG), a global method to assess coagulation status (Spiezia et al., 2020). In a recent report, it was shown that TEG parameters were consistent with a state of hypercoagulopathy in a series of 24 blood samples from ICU patients (Panigada et al., 2020). Of note, this hypercoagulability was not associated to a significant decrease in coagulation inhibitors such as antithrombin, protein C or protein S.

4. Thromboinflammation in Covid-19

Although one cannot exclude that the SARS-CoV-2 virus may have some direct procoagulant properties, the hemostasis abnormalities described above are thought to be largely related to the high-grade systemic inflammatory state characterizing severe Covid-19 patients (Connors and Levy, 2020). The concept of “cytokine storm” is associated with a marked increase in pro-inflammatory cytokines such as IL-1 and IL-6 and chemokines together with a Th1 response (England et al., 2020; Tay et al., 2020). The interplay between inflammation and thrombosis, also called thromboinflammation (or immunothrombosis), has been clinically recognized in different human pathologies including sepsis (for a recent review see Jackson et al., 2019). These intricate inflammatory and hemostatic reactions are part of an evolutionary conserved defense process against pathogens involving highly sophisticated molecular and cellular mechanisms in mammals. In this pathophysiological situation, several components of the coagulation system, the complement and the fibrinolytic system are involved in concert with endothelial cells, leukocytes and platelets activation (Jackson et al., 2019; Ekdahl et al., 2015).

A major cause of mortality in patients with Covid-19 is linked to acute lung injury related to ARDS. Several reports and observations suggest that the so-called “cytokine storm”, exacerbated by the lack of prior acquired immunity, is a major input for the occurrence of ARDS in Covid-19 patients (Coperchini et al., 2020). As mentioned above, PE and other mechanisms of pulmonary circulatory failure, such as thrombotic microangiopathy, may explain the relatively modest efficacy of standard prophylaxis with anticoagulants in severe Covid-19 patients (Litjos et al., 2020) and, in the most severe cases, the failure of standard assisted ventilation techniques.

The pathophysiology of ARDS in its early phase is known to combine local inflammation, the accumulation and activation of leukocytes and blood platelets, uncontrolled activation of coagulation and alteration of endothelial and epithelial permeability (Matthay et al., 2012; Washington et al., 2020). A pathology autopsy report on a small number of Covid-19 patients indicates the presence of pulmonary emboli and thrombotic microangiopathy restricted to the lung (Xu et al., 2020b). This study also reports the presence of platelet-rich clot formation and inflammatory cells (particularly neutrophils) aggregated with fibrin and platelets in small vessels. These features are consistent with a thromboinflammatory response associated with acute lung injury in Covid-19.

Blood platelets are anucleate cells released from megakaryocytes playing a key role in hemostasis in concert with plasma coagulation. Furthermore, it is now well recognized that platelets have important roles in the defense function and in the maintenance of vascular integrity (Koupenova et al., 2018; Rayes et al., 2019). A recent study also highlights their contribution to the protection of the epithelium of the pulmonary alveoli (Washington et al., 2020). Thrombocytopenia has been reported in ARDS (Yang et al., 2005). In Covid-19, thrombocytopenia, generally moderate, is a marker of severity of the disease (Lippi et al., 2020; Yang et al., 2020). A relevant hypothesis to explain thrombocytopenia and poor prognosis is consumption of platelets to form pulmonary thrombi (Thachil, 2020a; Xu et al., 2020a).

To contribute to our body's defense against infectious agents (viral, bacterial, or fungal) platelets are capable of interacting with leukocytes thus helping neutrophils extravasation on inflammatory sites, they also secrete cytokines (IL-1 β , TGF β , RANTES, sCD40L) and produce bioactive lipids (eicosanoids) modulating the inflammation (Koupenova et al., 2018; Rayes et al., 2019). In addition, during infection with the dengue virus it has been shown that the platelet inflammasome, still poorly characterized, is activated leading to the release of pro-inflammatory cytokines, in particular IL-1 β (Hottz et al., 2013). In a rat model of bacterial sepsis,

activation of the NLRP3 inflammasome in platelets has been associated with inflammation, increased vascular permeability and multi-visceral failure (Cornelius et al., 2019).

The interaction between platelets and neutrophils leads to their reciprocal activation and contributes to the release of chromatin and histone nets also called neutrophil extracellular traps (NETs) known to bind and immobilize pathogens. The secretion of histones amplifies the alteration of the alveolar endothelium and the NETs support the formation of thrombi (by activating platelets and the contact pathway of coagulation), thus increasing the risk of pulmonary microcirculation occlusion (Caudrillier et al., 2012).

In this context, it is important to note that the lung is, after the bone marrow, the richest organ in megakaryocytes and that in mice, the *in situ* platelets production in lungs is important (Lefrançois et al., 2017). Little is known about the physiological impact of this production in humans. Nevertheless, this recent discovery suggests that platelets are abundant in the alveolar tissue and that they can play a role in the pathophysiology of Covid-19, both in terms of protection by potential phagocytosis of the virus, and aggravation by amplifying local inflammatory processes and increasing the risk of occlusion of the pulmonary capillaries. A pathology report (Fox et al., 2020) shows megakaryocytes producing platelets within alveolar capillaries of Covid-19 patients. Whether this local production of platelets plays an important role following viral lung infection or during ARDS remains to be established. Overall, one can hypothesize that, during Covid-19, blood platelets are activated and recruited at the site of infection, particularly in the lungs, and participate in the activation of the inflammatory response as well as in the appearance of complications related to coagulopathy. Platelet studies in Covid-19 are currently lacking and would represent an important puzzle piece in our understanding.

Another important player in thromboinflammation is the endothelium. While the healthy endothelium is largely antithrombotic, under pathological conditions endothelium activation can lead to immune cells and platelets recruitment and activation (Yau et al., 2015). Endothelium activation and dysfunction has been described in severe Covid-19 patients (Escher et al., 2020). The ACE2 receptor is expressed on endothelial cells allowing direct infection by the SARS-CoV-2 virus leading to endothelial inflammation (endotheliitis) in several organs (Varga et al., 2020).

Following activation, endothelial cells are known to upregulate expression of adhesion molecules including VCAM-1, ICAM-1, and E-selectin that are important for leukocyte adhesion, activation and extravasation. Inflamed endothelial cells also express P-selectin and secrete VWF on their surface allowing platelet recruitment. Tissue factor (TF), a potent activator of coagulation, and plasminogen activation inhibitor 1 (PAI-1), blocking fibrinolysis, can be expressed by activated endothelium. TF is also known to be produced by activated monocytes leading to activation of the extrinsic coagulation cascade and α -thrombin generation. α -Thrombin is a key enzyme in fibrin generation but is also a potent platelet activator and has numerous effects on the vasculature (Jackson et al., 2019). The effects of α -thrombin are amplified by the reduction of endothelial antithrombotic actions of molecules such as thrombomodulin, of the activated protein C pathway and of tissue factor pathway inhibitor (TFPI). Activated platelets further interact with leukocytes, secrete proinflammatory molecules and polyphosphates that promote the contact phase of the coagulation pathway. Platelets aggregate via integrin GpIIb/IIIa activation and their surface become procoagulant through phosphatidylserine expression. α -Thrombin being able to enhance its own generation via different mechanisms and the endothelium having downregulated its natural antithrombotic properties, microvascular thrombosis and inflammation will further propagate.

Activation of the complement system (observation of deposit of the complement components C5b-9 and C4d in the microvasculature) may also contribute to microvascular injury and thrombosis in the pathogenesis of severe Covid-19 as suggested in a short series of patients (Magro et al., 2020).

Thus, endothelial cells, platelets and leukocytes in concert with the blood coagulation cascades are critical players of the thromboinflammatory reaction leading to thromboembolic events in severe Covid-19 patients (Fig. 1). These mechanisms are even further amplified by hypoxia and decreased blood flow.

5. Current treatment, bleeding risk and new perspectives

Following observations of a high incidence of venous thrombosis linked to mortality in severe Covid-19 patients admitted to the hospital, the thromboprophylaxis has been defined as standard care (Thachil et al., 2020b,c; Klok et al., 2020a,b; Tang et al., 2020b; Ti et al., 2020; Llitjos et al., 2020; Helms et al., 2020; Wichmann et al., 2020; Bikdeli et al., 2020). The heparin prophylactic treatment is associated with a better outcome in critically ill patients with high sepsis induced coagulopathy (SIC) score ≥ 4 , and with D-Dimers $> 0.3 \mu\text{g/mL}$ (Tang et al., 2020b). This study however shows some potential biases (observational study without propensity score, no mortality difference in entire cohort but in subgroup analysis) making definitive conclusions difficult.

Interestingly, in addition to the antithrombotic effect, the anti-inflammatory function of heparin may be relevant in this setting. Heparan sulfate proteoglycans bind to SARS-CoV2 spike proteins and may decrease binding to host protein, and reduce the proinflammatory activities of damage associated molecular patterns (DAMPs), chemokines, neutrophil chemotaxis and leukocyte migration (Thachil, 2020b; Liu et al., 2020; Lindahl and Li, 2020). Using surface plasmon resonance, it was shown that SARS-CoV-2 Spike S1 protein binds to heparin inducing a structural change (Mycroft-West et al., 2020).

In a meta-analysis concerning the effectiveness and safety of heparins for the prevention of venous thromboembolism in acutely ill patients (Alikhan et al., 2014), heparins, among 16 reported studies, reduced the incidence of thrombosis with a slightly stronger decrease in the low molecular weight heparin (LMWH) group compared to the unfractionated heparin (UFH) one. However, no significant difference between UFH and LMWH was observed in the incidence of PE. The authors found no clear difference in all-cause mortality but they specified that the studies were not powered to show a difference in mortality.

Several studies report high incidence of venous thrombosis arising in Covid-19 patients hospitalized in ICU units, or with higher risks factors of venous thrombosis such as obesity (BMI $> 30 \text{ kg/m}^2$), despite using standard venous thromboembolism thromboprophylaxis according to the ESC or ASH guidelines (Kostantidines et al., 2019; Schünemann et al., 2018; Poissy et al., 2020;

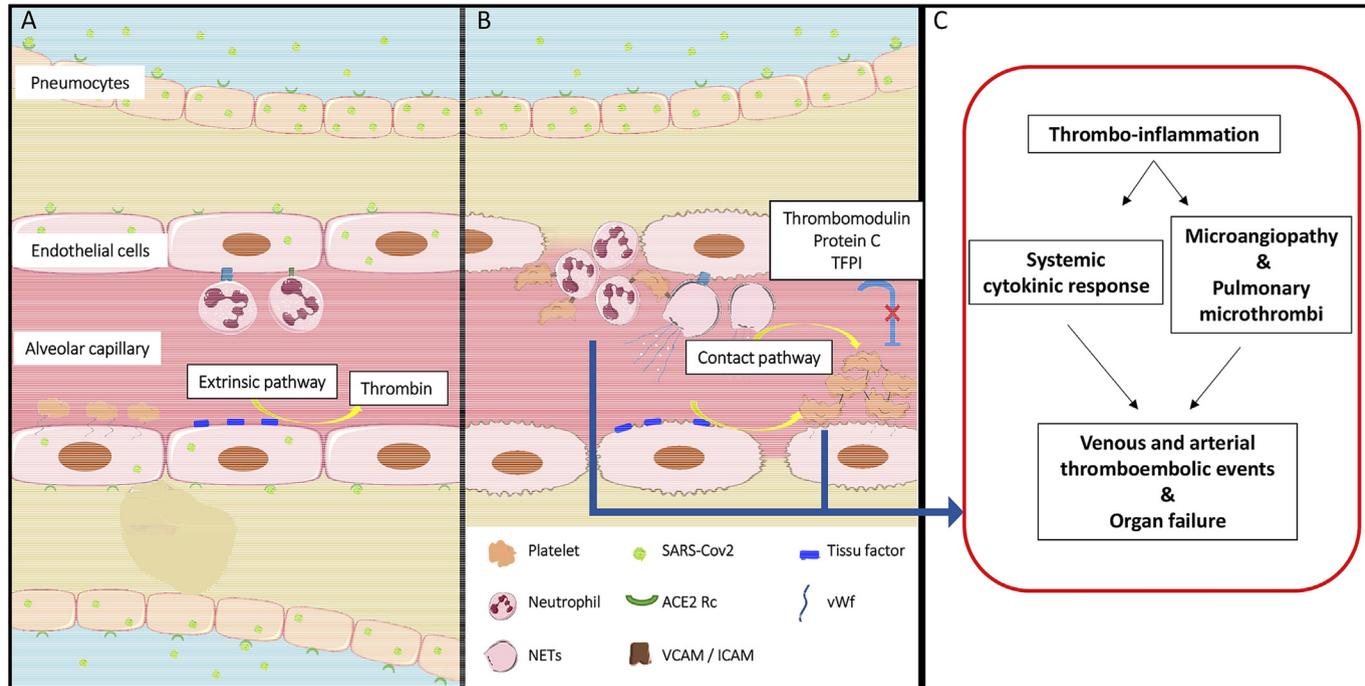


Fig. 1. Immunothrombosis mechanisms in pulmonary circulation during SARS-CoV-2 infection. **A.** Recruitment phase. SARS-CoV2 infects the alveolar epithelium and endothelial cells through binding to the ACE2 receptor (ACE Rc) exposed at the surface of these cells. Activation of endothelial cells by SARS-CoV-2 upregulates the externalization of Von Willebrand factor (vWF) and leukocytes' adhesion molecules (i.e. ICAM-1 (Intercellular Adhesion Molecule 1), VCAM-1 (Vascular cell adhesion protein-1), E-selectin) allowing adhesion of platelets and neutrophils. Activation of endothelial cells also triggers expression of tissue factor (TF) activating the extrinsic coagulation pathway and in turn α -thrombin generation leading to fibrin generation and platelets activation. **B.** Activation phase. Activated platelets interact with neutrophils leading to mutual amplification of neutrophil and platelet activation and eventually formation of Neutrophils Extracellular Traps (NETs) by DNA decondensation and externalization, allowing activation of the contact pathway. Thrombin generation through Tissue Factor (extrinsic) and contact pathways lead to clot formation and microvascular occlusion. Furthermore, clots are stabilized by the downregulation of endothelial antithrombotic properties. Meanwhile, cytokine release is triggered by platelets and leukocytes. **C.** Schematic representation of the systemic consequences of microvascular thromboinflammation. *This figure was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; <https://smart.servier.com>.*

Middledorp et al., 2020). The use of LMWH is proposed for all patients except those with severe renal impairment. For those patients, the prophylactic anticoagulant treatment is proposed with 5000 or 7500 unfractionated heparin (UFH) twice a day (Thachil et al., 2020b,c; Cohoon et al., 2020). Several authors suggest the use of a thromboprophylactic strategy with LMWH at low or intermediate dose (i.e. enoxaparin 4000 IU once, or twice daily if BMI > 30 kg/m²) (Fogarty et al., 2020; Cohoon et al., 2020; Spyropoulos et al., 2020). The optimal thromboprophylaxis in Covid-19 patients is unknown (Hunt et al., 2020) and in absence of published results of randomized studies, many prophylactic strategies based on international, national or institutional expert consensus (Marietta et al., 2020; Susen et al., 2020; Cohoon et al., 2020; Khider et al., 2020) have been suggested in order to manage the risk of venous thrombosis. All these strategies take into account the personal risk factors such as obesity (BMI > 30 or > 40 kg/m²), active cancer, previous venous thrombosis, age > 60 years, to consider the increase in treatment intensity in the higher risk patients. Even in outpatients with at least one risk factor of venous thrombosis, a thromboprophylaxis is proposed with prophylactic or intermediate doses. According to the VTE risk, the heparin treatment may be considered for up-to 45 days after hospital discharge (Paranjpe et al., 2020). Several authors specify that their guidance documents may be frequently updated. Many clinical trials are ongoing in the Covid-19 in the field of thromboprophylaxis.

It is noteworthy that some cases of thrombotic Heparin Induced Thrombocytopenia (HIT) were reported in Covid-19 patients (3 cases in a small series of patients with ARDS but only one confirmed by serotonin release assay) (Riker et al., 2020). The diagnosis of this rare immune complication of heparin treatment may be difficult in Covid-19 patients, particularly in ICU patients who have frequent thrombotic events and a mild thrombocytopenia.

When they are hospitalized, patients on long-term anticoagulation with oral anticoagulants, vitamin K antagonists (VKA) or direct oral anticoagulants (DOAC) should be switched to full-dose parenteral anticoagulation (mainly LMWH). Besides logistical challenges, such as drug intake difficulties or frequent INR monitoring for VKA, pharmacokinetics interactions of oral anticoagulants with multiple treatments, notably the antiviral therapies (lopinavir, ritonavir, darunavir) substrates of the P-glycoprotein and/or CYP3A4 make uncertain both their efficacy and safety (Testa et al., 2020; Cohoon et al., 2020; Khider et al., 2020; Susen et al., 2020).

Drug-drug interaction (DDI) may affect the levels of active metabolites of P2Y12 antagonists and protease inhibitors in patients requiring a double antiplatelet therapy. When an investigational antiviral treatment is introduced, the choice and the dose of P2Y12 antagonist agents should be carefully balanced in terms of benefit-risk at the lumen of pharmacokinetics of each drug. For example, ritonavir decreases the levels of active metabolites of the prodrug thienopyridines (clopidogrel, prasugrel) and thereby reduces their efficacy. Conversely, ritonavir increases the levels of ticagrelor, which is directly active but metabolized by CYP3A4, and thereby increases the bleeding risk (Itkonen et al., 2019; Ancrenaz et al., 2013; Marsousi et al., 2016). Remdesivir is an inducer of CYP3A4 but dose adjustments for oral antiplatelet agents is currently not recommended. Of note, there are no major DDI between investigational Covid-19 therapies and parenteral antiplatelet agents such as cangrelor and integrin GpIIb/IIIa inhibitors (Bikdeli et al., 2020).

A few anecdotal reports on fibrinolytic off-label intravenous administration (tPA) in Covid-19 ICU patients have shown transient pulmonary perfusion improvement (Wang et al., 2020b). The diagnosis of DIC is probably overestimated in Covid-19 (Escher et al., 2020). In case of DIC, the management follows the basics principles.

Clinically-overt bleeding is uncommon in the setting of Covid-19. In summary, the mainstay of blood product transfusion is as follows: i) platelet concentrate to maintain platelet count > 50 G/L in DIC patients with active bleeding or > 20 G/L in those with a high risk of bleeding or requiring invasive procedures, ii) fresh frozen plasma (FFP) (15–25 mL/kg) in patients with active bleeding with either prolonged PT and/or APTT ratios (> 1.5 times normal) or decreased fibrinogen (< 1.5 g/L) and iii) fibrinogen concentrate to patients with persisting severe hypofibrinogenemia (< 1.5 g/L). With the existing data, tranexamic acid, which suppresses the conversion of plasminogen to plasmin, should not be used routinely in Covid-19-associated DIC. However, it should be noted that some clinical trials (NCT04390217; NCT04338074; NCT04338126) evaluate tranexamic acid use in order to reduce the virulence of SARS-CoV-2 because plasmin has been proposed to cleave a viral protein resulting in increased infectivity.

6. Conclusion

During the past six months, on the base of early pre-published experience, our knowledge on the pathophysiology of severe forms of the disease has rapidly evolved towards a systemic inflammatory storm with vascular changes in multiple organs particularly in the lungs. Covid-19 is challenging many clinicians and researchers worldwide to better understand the pathophysiology of the disease, particularly of the ARDS and the thromboinflammatory state. The cytokinic storm mainly described in severe patients may contribute to thrombogenicity and to multiple organ failure leading to death. Many publications report an unusual high incidence of thromboembolic events increasing mortality. Disturbed hemostasis parameters are observed, and coagulopathy is associated with poor outcome, emphasizing the importance to monitor biological and hemostatic changes during the course of the disease. Thromboprophylaxis is a standard of care even if adjustments seem necessary in patients with previous risk factors of thromboembolic disease. Whereas the pandemic Covid-19 is declining, at least in Asia and Europe, more than 1300 clinical trials, one-fourth in the setting of ICU, are registered in the World Health Organization's International Clinical Trials Registry Platform. No doubt that new data will be published in coming months/years, with possible changes in our perception of the disease, its prevention and treatments. This is clearly necessary to improve Covid-19 patient's prognosis.

Declaration of competing interest

The authors declare no competing financial interests.

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